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# OXYGEN-ATOM TRANSFER CHEMISTRY OF α-AZO HYDROPEROXIDES: EFFECT OF COMPETITIVE INTRAMOLECULAR HYDROGEN BONDING AND α-METHYL SUBSTITUTION

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## ABSTRACT

1-(Phenylazo)-1-(2-pyridyl)ethyl hydroperoxide, **1**, 1-(phenylazo)-1-(2-furyl)ethyl hydroperoxide, **2**, phenylazo(2-furyl)methyl hydroperoxide, **3**, 1-(phenylazo)-1-(4-anisyl)ethyl hydroperoxide, **4**, were synthesized in moderate yield by autoxidation of the phenylhydrazones in benzene. The ionic oxidation of benzyl methyl sulfide in benzene by **1–4** yielded the sulfoxide and the metastable α-azo hydroxides in essentially quantitative yield. The reaction was of the first order in α-azo hydroperoxide and sulfide, respectively. The relative reactivity series found was: **1**(1.0) <**4**(1.4) < phenylazo(4-anisyl)methyl hydroperoxide **5** (2·9) <**2** (3·8) < **3** (9·6). α-Methyl substitution was found to slow the rate of oxygen-atom trasfer by a factor of 2 to 2·5. The low relative reactivity of **1** was opposite that expected based on electronic effects. Competitive intramolecular hydrogen bonding of the hydroperoxy proton to the pyridyl nitrogen in **1** accounted for the observed result.

Hydroperoxides are important reagents for the oxidation of many classes of organic compounds. Organic hydroperoxides are able to transfer oxygen atoms by electrophilic pathways[1] as well as free-radical and related metal ion catalyzed processes. Our recent work[2] has shown that a class of 'alkyl' hydroperoxides, α-azo hydroperoxides or α-peroxydiazatenes[3] [$R_1R_2$—C(OOH)—N=N—$R_3$], are of high reactivity in electrophilic (ionic) oxygen-atom transfer reactions, reaction (1), in aprotic media. Cyclic α-azo hydroperoxides[4] are of similar reactivity[5] to that of flavin 4a-hydroperoxides[6] and roughly two orders of magnitude more reactive than acyclic analogues.[7]

$$R_1R_2\text{—C(OOH)—N=N—}R_3 + :X \xrightarrow{k_2} R_1R_2\text{—C(OH)—N=N—}R_3 + 0 = X \qquad (1)$$

Interestingly, for α-azo hydroperoxide ionic oxidations, selectivity has been found to be essentially invariant (and at a maximum), independent of hydroperoxide structure and reactivity.[2,8] Mechanistically, the electrophilic oxygen-atom transfer reactions of α-azo hydroperoxides have been rationalized to occur via a concerted mechanism in which the transition state requires partial intramolecular transfer or hydrogen bonding of the hydroperoxy proton to a nitrogen atom during nucleophilic attack of the substrate on the terminal oxygen atom. An isotope effect study[9] with deuteration of the hydroperoxy proton yielded values of $k_H/k_D$ of 1·3±0·1 for the rates of oxidation of alkenes, sulfides, and amines

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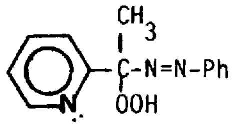
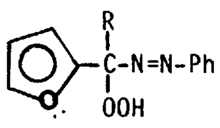
consistent with expectations. We report here a study of the effect of competitive intramolecular hydrogen bonding sites and α-methyl substitution on oxygen-atom transfer capabilities of α–azo hydroperoxides.

## RESULTS

New α-azo hydroperoxides [1-(phenylazo)-1-(2-pyridyl)ethyl hydroperoxide, **1**, 1-(phenylazo)-1-(2-furyl)ethyl hydroperoxide, **2**, phenylazo(2-furyl)methyl hydroperoxide, **3**, 1-(phenylazo)-1-(4-anisyl)ethyl hydroperoxide, **4**] were synthesized (*caution!*) in moderate

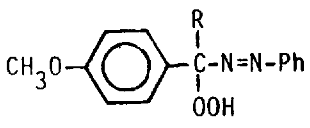


**1**



**2** R=$CH_3$

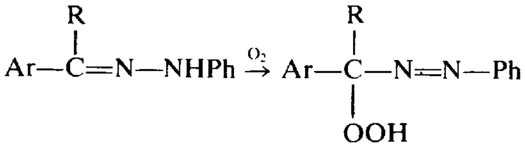
**3** R=H



**4** R=$CH_3$

**5** R=H

yield by the autoxidation of the corresponding phenylhydrazones, reaction (2), in benzene under pressure. α-Azo hydroperoxide **5** has been

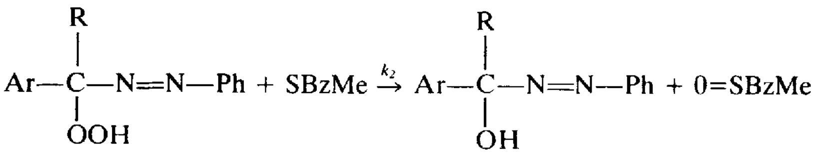


$$\mathrm{Ar{-}\overset{\displaystyle R}{\overset{|}{C}}{=}N{-}NHPh} \xrightarrow{O_2} \mathrm{Ar{-}\underset{\displaystyle OOH}{\underset{|}{\overset{\displaystyle R}{\overset{|}{C}}}}{-}N{=}N{-}Ph} \tag{2}$$

**1–5**

previously reported [7a] and was included for comparisons. Compounds **1** and **4** were isolated in crystalline form (*caution*!) and were characterized by spectroscopic and physical methods. The furyl-substituted compounds **2** and **3** did not crystallize and were found to be extremely unstable unless kept in solution (benzene). Compounds **2** and **3** were characterized by spectral methods and by analysis of the decomposition products.

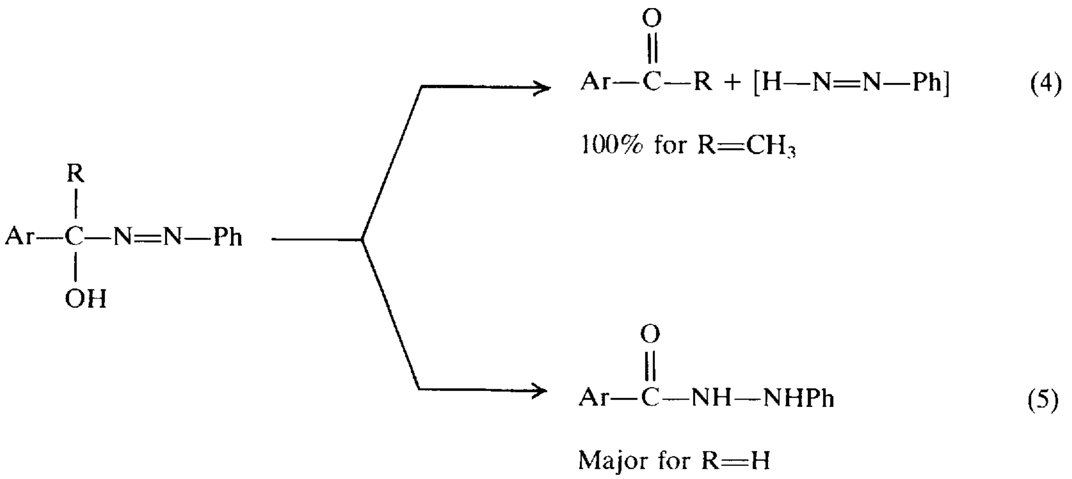
The oxygen-atom transfer reactions of **1–4** with benzyl methyl sulfide in benzene yielded the metastable α-azo hydroxides and the sulfoxide in essentially quantitative yields in all cases, reaction (3). The α-azo hydroxides,



$$\mathrm{Ar{-}\underset{\displaystyle OOH}{\underset{|}{\overset{\displaystyle R}{\overset{|}{C}}}}{-}N{=}N{-}Ph + SBzMe} \xrightarrow{k_2} \mathrm{Ar{-}\underset{\displaystyle OH}{\underset{|}{\overset{\displaystyle R}{\overset{|}{C}}}}{-}N{=}N{-}Ph + 0{=}SBzMe} \tag{3}$$

metastable

observed by $^1$H-NMR spectroscopy, were stable for several hours. Undisturbed, these compounds underwent slow decomposition to secondary products, reactions (4) and (5), with gas evolution ($N_2$) over the course of one or two days. α-Azo hydroxides with R=$CH_3$ decomposed quantitatively to the aryl methyl ketones, reaction (4), and presumably phenyldiimide (not observed). Once formed, phenyldiimide would be expected to undergo rapid decomposition to benzene with evolution of $N_2$ (consistent with the observations). For α-azo hydroxides with R=H, the major decomposition products were the hydrazides, reaction (5).[8] The aryl methyl ketones, hydrazides, and sulfoxides were isolated and identified by comparison with authentic samples.

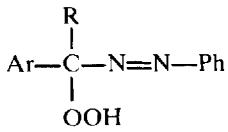


The oxidation of benzyl methyl sulfide by **1**–**5** in benzene-$d_6$ at 34 °C was found to be of the first order in sulfide and α–azo hydroperoxide, respectively in the aprotic medium. The second order rate constants were determined ($^1$H-NMR spectroscopy) by monitoring the rate of appearance of sulfoxide and/or the rate of disappearance of α-azo hydroperoxide vs added internal standard. α-Methyl substitution was found to slow the rate of oxygen atom transfer by a factor of 2 to 2·5. Compound **1** was the least reactive hydroperoxide of this series while **3** was the most reactive. The relative reactivity series was: **1** < **4** < **5** <**2** < **3**. The results are summarized in Table 1.

The reduced reactivity of **1** was surprising. Control experiments in which one equivalent of pyridine was added to **4** or **5** in benzene showed that the rate of oxidation of benzyl methyl sulfide slowed by approximately a factor of 2 (no N-oxidation was observed). Addition of one equivalent of acetic acid to S-oxidation by **1** or by **4** and **5** in the presence of pyridine yielded $k_2$ values that were increased by approximately an order of magnitude. The results are listed in Table 2.

In addition, compounds **1** and **4** were found to oxidize triethylamine to the N-oxide in high yield ($k_2$ for **4** of $3{\cdot}3 \pm 0{\cdot}1 \times 10^{-4}\,\mathrm{M}^{-1}\mathrm{s}^{-1}$). However, α–azo hydroperoxide **5** with R=H underwent rapid decomposition in the presence of triethylamine with little resultant N-oxidation (~6%) to yield mainly azo ketone [Ar—CO—N=N—Ph] and carboxylic acid (Ar—$CO_2$H) as products. Presumably these latter products arise via amine-catalyzed removal of the α-proton with loss of hydroxide to yield azo ketone (subsequent partial hydrolysis of which by traces of water would produce the corresponding acids). Tezuka has postulated[10]

Table 1. Rate constants for oxidation of BzSMe by **1–5** in benzene at 34 °C



$$\mathrm{Ar{-}\underset{\displaystyle OOH}{\overset{\displaystyle R}{C}}{-}N{=}N{-}Ph}$$

| Peroxide | Ar | R | $k^2$(M$^{-1}$s$^{-1}$) | relative reactivity |
|---|---|---|---|---|
| **1** | 2-pyridyl | Me | 2·5 ± 0·3 × $10^{-3}$ | 1·0 |
| **2** | 2-furyl | Me | 9·4 ± 0·9 × $10^{-3}$ | 3·8 |
| **3** | 2-furyl | H | 2·4 ± 0·5 × $10^{-2}$ | 9·6 |
| **4** | 4-anisyl | Me | 3·4 ± 0·1 × $10^{-3}$ | 1·4 |
| **5** | 4-anisyl | H | 7·2 ± 0·3 × $10^{-3}$ | 2·9 |

Table 2. Effect of added acetic acid and pyridine on the rate constants for oxidation of BzSMe by **1**, **4**, and **5** in benzene at 34 °C

| Peroxide | [Peroxide]$_0$ | [HOAc]$_0$ | [Pyridine]$_0$ | $k_2$(M$^{-1}$s$^{-1}$) | Rel Effect[a] |
|---|---|---|---|---|---|
| **4** | 0·17 | -- | 0·17 | 1·7 ± 0·1 × $10^{-3}$ | 0·5 |
| **4** | 0·14 | 0·14 | 0·14 | 1·5 ± 0·1 × $10^{-2}$ | 4·4 |
| **5** | 0·11 | -- | 0·11 | 2·7 ± 0·2 × $10^{-3}$ | 0·4 |
| **5** | 0·11 | 0·11 | 0·11 | 4·4 ± 0·4 × $10^{-2}$ | 13 |
| **1** | 0·13 | 0·14 | -- | 3·2 ± 0·2 × $10^{-2}$ | 13 |

[a] $k_2$ from table 2/$k_2$ from Table 1.

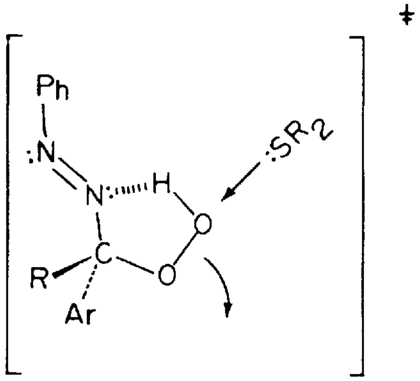
other routes to explain similar products in 'pyridine-catalyzed' α-azo hydroperoxide oxidation reactions. Interestingly, for **1** self-oxidation of the pyridyl substituent was not observed.

## DISCUSSION

Prior work[7a] on the oxidation of benzyl methyl sulfide by a series of phenylazo(aryl)methyl hydroperoxides yielded excellent correlations of $k_2$ values with sigma constants: rho of +1·08. The decrease in relative reactivity upon formal α-methyl substitution (**2** vs **3** and **4** vs **5**) is consistent with expectations based on 'inductive' effects. However, the contributions of steric (eclipsing) interactions, if any, are difficult to assess and cannot be ruled out. Similarly, the 3-fold greater relative reactivity of the furyl compounds (**2**, **3**) as compared to that of the anisyl compounds (**4**, **5**) is in accord with predictions based on Hammett-type parameters. However, the results for **1** are not consistent with inductive effects. The 2-pyridyl substituent would be expected to result in an, at least, ten-fold greater reactivity than that of **2** rather than the four-fold decrease observed.

Tezuka has postulated [10a] the formation of N-substituted peroxycarboximidic acids in the pyridine-catalyzed oxidations of α-azo hydroperoxides with α-protons. This type of reactive intermediate could not form for α–methyl compounds **1**, **2** and **4**, but must be considered for compounds **3** and **5**. Addition of one equivalent of triethyl amine (strong base) to **5** (or **3**) resulted in the rapid decomposition and a product distribution similar to those observed [10a] by Tezuka for the slow (days) pyridine-catalyzed decompositions of similar compounds. Addition of one equivalent of pyridine to **5** resulted in only 9% loss of starting hydroperoxide after 4 hrs at 34 °C. Subsequent addition of sulfide resulted in slower than normal S-oxidation, yielding the same $k_2$ value as if all the reagents were mixed together initially. Under the conditions of our experiments, N-substituted peroxycarboximidic acids appear not to be involved.

Scheme 1[a]



[a] Five-membered intramolecular hydrogen-bonded transition state shown for convenience.

A likely explanation for the unusually low relative reactivity of **1** involves competitive intramolecular hydrogen bonding of the hydroperoxy proton to the pyridyl substituent which disrupts the normal transition state for S- oxidation (Scheme 1).[7a] Solvent effect studies have shown [7b] the competitive intermolecular hydrogen bonding to acetonitrile resulted in greatly reduced rates of oxygen-atom transfers. $^{17}$O-NMR studies on $^{17}$O-enriched α-azo hydroperoxides showed chemical shift differences upon differential hydrogen bonding. Interestingly, this interpretation of the results requires that the six-ring intramolecular hydrogen bond to the pyridyl group in **1** does not allow oxygen-atom transfer or at least is much slower than the normal situation. The presence of one equivalent of added pyridine in S-oxidations with 'normal' α-azo hydroperoxides slowed the reactions by a factor of approximately 2. This suggests that intermolecular hydrogen bonding of the hydroperoxy proton is competitive with the normal intramolecular hydrogen-bonding situation required for reaction. Experiments in which acetic acid is added appear to reverse the inhibiting effect of the pyridyl group or added pyridine and support the competitive hydrogen bonding argument. However, acid catalysis[7a] of S-oxidation may also be involved, complicating the interpretation. The relative reactivity data for **2** and **3** suggests that intramolecular hydrogen bonding of the hydroperoxide to the furyl oxygen may not be competitive with the hydrogen bonding to the azo function.[9]

The presence of a strong intramolecular or intermolecular hydrogen bond acceptor slows the oxygen-atom transfer reactions of α-azo hydroperoxides. Apparently, any disruption of the intramolecular hydrogen bond to the azo function leads to pathways in which oxygen-atom transfer is slower than the normal situation.

## EXPERIMENTAL SECTION

All solvents were of reagent grade. Benzyl methyl sulfide, 2-acetylpyridine, 2-acetylfuran, fufural, and *p*-methoxyacetophenone were available commercially and were distilled if necessary before use. Phenylazo(*p*-anisyl)methyl hydroperoxide **5** was prepared according to published procedure[7a] (*Caution*! Danger of explosion!). $^1$H-NMR spectra were taken on a Varian EM360L spectrometer while $^{13}$C-NMR spectra were taken on a JEOL GX-270 spectrometer. Analyses were performed at Atlanta Microlabs, Atlanta, GA.

### Synthesis of α-azo hydroperoxides

*1-(Phenylazo)-1-(2-pyridyl)ethyl hydroperoxide* **1** was synthesized by autoxidation of the purified phenylhydrazone of 2-acetylpyridine in benzene under pressure (*Caution* ! Extreme danger of explosion!). In a pressure bottle, 1·0 g of phenylhydrazone under 100 psi of pure oxygen in 25 ml dry benzene underwent complete autoxidation in the dark after 3 hrs at 10–15 °C. The solvent was removed under reduced pressure at *low* temperature in the dark. The resulting residue was crystallized from ether-petroleum ether at low temperature to yield 0·65 g of orange crystals, 60% isolated yield: mp 91–93 °C (*Detonation* !); Analysis found C-64·10, H-5·43, N-17·25 calculated C-64·18, H-5·39, N-17·27; $^1$H-NMR ($C_6D_6$) δ 2·08 (s, 3H), 6·33–6·63 (m, 1H), 6·98 (m, 5H), 7·6 (m, 2H), 8·3 (m, 1H), 10·47 (s, 1H); $^{13}$C-NMR, 158·0 (q), 152·1 (q), 149·1, 136·7, 131·6, 129·5, 123·9, 123·5, 122·9, 105·8 (q), 20·3. Small samples of **1** could be stored at −70 °C in the dark as the solid, with no apparent difficulties; however, solution storage is suggested. α-Azo hydroperoxides **2**, **3** and **4** were synthesized as above with the following modifications: 0·5 g of phenylhydrazone in 5 ml of benzene and with reaction times of 5, 6 and 3 hrs, respectively, $^1$H-NMR spectra ($C_6D_6$) for **2** δ 1·95 (s, 3H), 5·95 (m, 1H),6·23 (s, 1H), 6·9–7·7 (m, 6H), ~9 (br.s., 1H); for **3** δ 5·90 (m, 2H), 6·33 (d, 1H), 6·77–7·20 (m, 4H), 7·53–7·70 (m, 2H), 9.3 (br.s., 1H); for **4** δ 1·95 (s, 3H), 3.23 (s., 3H), 6·87 (d, 2H), 6·95–7·10 (m, 3H), 7.40–7·67 (m, 4H), 9.45 (s, 1H). Compounds **2** and **3** were oils and extremely unstable if neat. Compound **4** crystallized at −70 °C but melted below room temperature. **2–4** were stored at −70 °C in benzene-$d_6$ in the dark. α-Azo hydroperoxides of these types were found to be light sensitive. In addition, several samples *detonated*(!) when pure and dry. Work should only be carried out on a small scale (<1g) and the compounds should be stored and handled in solution whenever possible.

### Kinetic and product studies

The following general procedure was employed for all kinetic experiments. A sample of pure α-azo hydroperoxide (~0·03 mmol) was placed (in the dark) in a new 5 mm NMR sample tube with 0·500 ml of benzene-$d_6$ (Merck) containing anisole or *t*-butylbenzene as internal standard. After the $^1$H-NMR spectrum was recorded, the desired quantity of benzyl methyl sulfide (or other reactant) was added to the solution and mixed. The $^1$H-NMR signals were recorded and integrated vs time. Rate data, determined by monitoring the appearance of sulfoxide and/or the disappearance of hydroperoxide relative to internal standard, yielded identical rate constants. The kinetic data were obtained for at least 2 half-lives and yielded excellent correlation coefficients (>0·99, all cases).

The yield of sulfoxide and metastable α-azo hydroxide was quantitative (95±5%) relative to internal standard. The sulfoxide was isolated and the structure proven by comparison with an authentic sample. The α-azo hydroxides corresponding to compounds **1**, **2** and **4** underwent slow decomposition with evolution of gas to yield 2-acetylpyridine, 2-acetylfuran, and *p*-methoxyacetophenone, respectively. The gas, presumably, was nitrogen arising from the fast thermolysis of other α-azo hydroxide decomposition product, H—N═N—Ph. The carbonyl containing decomposition products were isolated and identified by comparison with authentic samples.

## ACKNOWLEDGMENT

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